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Increased non-eosinophilic nasal polyps in chronic rhinosinusitis in U.S. second-generation Asians suggests genetic regulation of eosinophilia

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Capsule Summary

In this study we found a significantly lower eosinophilia in nasal polyps surgically removed from second-generation Asian patients, similar to studies of native-born patients in Asian countries, suggesting the hypothesis that there may be genetic regulation of eosinophilia.

Keywords

Chronic Rhinosinusitis; Nasal polyp; Non-eosinophilic; Ethnicity; Asian; Genetic

To the Editor,

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory disease with high impact on quality of life and is characterized by presence of polyps in an individual with diagnosis of chronic rhinosinusitis. While the majority of nasal polyps (NP) in CRSwNP patients seen in western countries are eosinophilic (1, 2) non-eosinophilic NP comprise a significant percentage of CRSwNP seen in East Asian countries including China, Korea, Japan and Malaysia (3–8). Studies comparing polyps in Chinese and Belgian patients have shown significantly lower eosinophil numbers (3, 9) and lower Eosinophil Cationic Protein (ECP) levels (9) in NP in Chinese patients.

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In the last decade, there has been a trend toward increasing eosinophilic nasal polyposis in Asian populations (5, 10R). A Korean study has shown that eosinophilic nasal polyps have increased from 24% of total nasal polyps resected in 1993–4 to 50.9% in 2010–12 (5). However, recent studies still show that about half of CRSwNP cases in East Asian countries have a non-eosinophilic pathology (4–8). This raises the possibility that this type of nasal polyps are influenced by different pathogenesis elements that are more common in that area and/or that genetic factors play a role in the level of eosinophilia in nasal polyps in Asian populations.

In an attempt to test whether the propensity of Asian populations to manifest non-eosinophilic polyps is due to genetic factors, we evaluated the eosinophilic marker ECP and evidence for eosinophilia in the pathology report of polyp and sinus tissue collected during FESS surgery in a group of second-generation Asian CRS patients in Illinois, and compared them with Illinois patients of other ethnicities. We focused upon study patients with both parents from Asian countries that were born and raised in the US. Such patients come from the same genetic pool as their parents but have presumably been exposed to environmental factors present in the US. Our findings demonstrated reduced eosinophilia in Asian CRSwNP patients that were born and raised in the U.S.

A consecutive series of 296 CRSwNP patients who underwent surgery at Northwestern University from 2005 to 2013 were included. Patients with self reported Asian ancestry and born in the US, were identified as second-generation Asian. Twenty-three patients had identified themselves as Asian (including Chinese, Korean, Japanese and Malaysian), out of which 11 were second generation and were included. The rest were excluded from the study. Original pathology reports of polyp and sinus tissue obtained during surgery were reviewed for reported eosinophilia. The tissue would have been reported as eosinophilic by the pathologists if eosinophils comprised more than 10% of inflammatory cells in the studied area. Furthermore, in 161 of the enrolled cases, tissue homogenates of polyp and/or uncinate tissue (UT) were available in a prospectively collected biorepository and were analyzed for ECP. UT was used as representative of sinus and upper nasal tissue. Previous studies have shown that the nasal polyps and UT of CRSwNP patients from the US have significantly higher numbers of eosinophils compared to control UT (2). ECP levels were measured by ELISA using the Mesacup ECP Test Kit from MBL, Woburn, MA. The ECP concentration was measured as ng/μl. The level was adjusted to total protein concentration in each sample which was measured as mg/μl. All ECP levels were reported as ng/mg of total protein. Physician diagnosis of asthma and atopy were recorded as part of the study and were double-checked by chart review. Atopy was defined by evidence of allergic sensitization to aeroallergens by skin prick test or Immunocap testing. The study was approved by the Northwestern University institutional review board.

Comparisons among groups in terms of ECP levels were assessed by Kruskal-Wallis and Dunn's multiple comparisons tests. Comparisons between groups in terms of eosinophilic polyps, asthma and atopy were done by Fisher's exact test. Adjusting for age and gender for the above analyses was performed by logistic regression. These statistical analyses were performed using IBM SPSS version 22. A p-value of less than 0.05 was considered statistically significant.

Levels of ECP in polyp (mean 179.4 ng/mg vs. 1256 ng/mg; $P<0.001$) and UT samples (mean 133.6 ng/mg vs. 838.6 ng/mg; $P<0.001$) were significantly lower in tissue from second generation Asian versus non-Asian patients (not shown). Further comparison of Asian patients with patients of European descent (Caucasian), African Americans and Hispanics showed that Asian patients had lower ECP levels in polyp extracts compared to all of these groups, but the difference only reached statistical significance compared to European patients (fig. 1A). As with the polyp tissue, the ECP level in UT of Asian cases was significantly lower compared to ECP in UT extracts of European patients (fig. 1B).

Per pathology reports, 27% of polyp/sinus tissues from Asian patients were eosinophilic as opposed to 65% in patients of European descent, 70% in Hispanics and 62% in African American patients (fig. 1C; $P<0.05$ for all comparisons). The ECP levels in both polyp and UT were significantly higher in those cases reported to have eosinophilia in the pathology report (fig. 1D).

Moreover, Asian patients had a significantly lower prevalence of atopy (fig. 1E) and a trend towards lower prevalence of asthma (fig. 1F) compared to patients of European descent and African American patients.

Although the mean age of the Asian group was about 10 years lower than patients of other ethnicities, this difference was not statistically significant (mean age of 36.80 years in Asians vs. 47.09, 47.10 and 43.12 in Caucasian, African Americans and Hispanic patients respectively). The Male to female ratio was also slightly higher in Asians (72% in Asians, 59% in Hispanic, 53% in African Americans and 60% in Caucasians), but this was not statistically different among various ethnicities. Age and gender were not associated with eosinophilic nasal polyps in general or in the individual populations. After adjusting the analyses for age and gender by logistic regressions, the associations between ethnicity, and ECP level, eosinophilia, and atopy remained significant (not shown).

The difference between eosinophilic and non-eosinophilic polyps seems to go beyond the presence or number of eosinophils. A study comparing the histopathology of polyps from Asian patients with polyps from European patients has shown significant differences not only in eosinophil numbers but also in terms of the T-helper cells involved in tissue inflammation (9). Interestingly, observations within Asian populations have also shown different histologic characteristics and remodeling patterns in non-eosinophilic versus eosinophilic polyps in Chinese patients with CRSwNP (4,11R).

The infiltration of eosinophils in the mucosal membrane and polyps has also been linked to the clinical characteristics of the disease. Consistent with our results, other studies have shown that non-eosinophilic polyps are less frequently associated with atopy and asthma (8, 9, 12R). Furthermore, non-eosinophilic CRSwNP patients have a lower polyp recurrence rate (6) and are associated with a lower blood eosinophil count (8, 12R). It is noteworthy that the current practice in management of non-eosinophilic CRSwNP, which is primarily macrolide antibiotics, is different from eosinophilic CRSwNP where corticosteroids are the mainstay in treatment (13R)

These differences in the phenotype and outcomes of disease suggest that it is worthwhile understanding the differences in pathogenesis of non-eosinophilic and eosinophilic CRSwNP.

There is evidence for higher prevalence of non-eosinophilic polyps in Asian patients enrolled in this study. Although the higher prevalence of non-eosinophilic polyps in second-generation Asian patients is suggestive of a role of genetic factors that are present in Asian-descended subjects, environmental factors or genetic/environmental interaction effects cannot be excluded. Furthermore different underlying causes could influence the formation of non-eosinophilic polyps in Asians. Second generation immigrant populations may maintain diet and lifestyle factors that influence the phenotype of disease or may have stable differences in the microbiome, after immigration.

The magnitude of the difference uncovered in the present study suggests that a prospective cohort of Asian immigrants with long-term follow is worthwhile and can potentially evaluate the true prevalence of both types of nasal polyps in relation to lifestyle and genetic factors in this population. This could shed light on the pathogenesis and role of genetic and environmental risk factors influencing eosinophilia, CRSwNP in general and the relative paucity of eosinophilic polyps in Asians.

In conclusion, our study showed a significantly lower eosinophilia in nasal polyps surgically removed from second generation Asian patients. This is in line with studies conducted on native-born patients in Asian countries that showed up to half of the nasal polyposis patients have a non-eosinophilic histology. While future studies are needed to further elucidate these findings, our results are suggestive of possible genetic factors or genetic/environment interactions playing a role in the pathogenesis of non-eosinophilic nasal polyps.

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List of Abbreviations

CRS	Chronic rhinosinusitis
CRSwNP	CRS with nasal polyps
ECP	Eosinophil Cationic Protein
NP	Nasal polyp
UT	Uncinate tissue
R	references in the online repository material

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Figure 1.

Eosinophil Cationic Protein (ECP) in polyp tissue homogenates was significantly lower in samples from Asian patients compared to Caucasian patients (1A). Also the ECP level in UT of Asian cases was significantly lower compared to ECP in UT extracts of both Caucasian and African American patients (1B). Asian patients had a significantly lower frequency of pathology reported eosinophilic sinusitis compared to patients of other ethnicities (1C). The ECP level in polyp extracts was significantly lower in cases reported in the surgical pathology exam as non-eosinophilic compared to those reported as eosinophilic. (1D). Asian

patients with CRS and nasal polyposis had a significantly lower frequency of asthma (1E) and atopy (1F) compared to Caucasian and African American patients (* $p<0.05$).